Corrositex® Peer Review Meeting Summary Minutes

January 21, 1999
Bethesda, Maryland

Introduction

A public meeting of an independent peer review panel was convened on January 21, 1999, in Bethesda, Maryland to review Corrositex®, which was proposed as an alternative toxicological test method for assessing the corrosivity potential of chemicals and products. The meeting was coordinated by the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) and the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and was sponsored by the National Institute of Environmental Health Sciences (NIEHS) and the NTP.

The following expert scientists served on the peer review panel:

- Robert Scala, Ph.D., retired from Exxon Biomedical Sciences, Rehoboth Beach, Delaware (Panel Chair)
- Julia Fentem, Ph.D., Unilever Research Colworth, Bedfordshire, United Kingdom (Executive Secretary)
- James Chen, Ph.D., NCTR, Little Rock, Arkansas
- Michael J. Derelanko, Ph.D., Allied-Signal, Inc., Morristown, NJ
- Sidney Green, Ph.D., Howard University College of Medicine, Washington, D.C.
- John Harbell, Ph.D., Institute for In Vitro Sciences, Gaithersburg, Maryland
- A. Wallace Hayes, Ph.D., the Gillette Company, Boston, Massachusetts
- Karen Kohrman, Ph.D., the Procter & Gamble Company, Cincinnati, Ohio
- Hajime Kojima, Ph.D., Nippon Menard Cosmetic Company, Ltd., Nagoya, Japan
- Daniel Sauder, M.D., University of Toronto, Toronto, Ontario
- John Stegeman, Ph.D., Woods Hole Oceanographic Institution, Woods Hole, Massachusets

Meeting—Background Information

Introductions

Dr. Scala, chair, called the meeting to order at 8:30 a.m. and asked each person in attendance to state their name and affiliation.

Welcome from the National Toxicology Program

Dr. George Lucier, Director of the NTP, thanked the ICCVAM participating agencies and stakeholders, the Corrositex® Sponsor, and the peer review panel (PRP) for their efforts. Dr. Lucier also presented an overview of the NTP and the ICCVAM process.

Introduction to NICEATM and ICCVAM/ Overview of the Corrositex® Peer Review Process

Dr. William Stokes, ICCVAM Co-Chair and Director of NICEATM, explained the ICCVAM review process, and the steps that had been undertaken in the review of Corrositex®. He discussed the role of the ICCVAM committee, its expert subgroup (Corrosivity Working Group [CWG]), the peer review panel, and the process by which regulations are reviewed and forwarded to agencies for action.

Public Law 103-43 directed the NIEHS to develop and validate alternative methods that can reduce or eliminate the use of animals in acute or chronic toxicity testing, establish criteria for the validation and regulatory acceptance of alternative testing methods, and recommend a process through which scientifically validated

alternative methods can be accepted for regulatory use. Criteria and processes for validation and regulatory acceptance were developed in conjunction with 13 other Federal agencies and programs with broad input from the public. These are described in the document "Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the Ad Hoc Interagency Coordinating Committee on the Validation of Alternative Methods," NIH Publication 97-3981, March, 1997. This document is available in the internet at http://ntp-server.niehs.nih.gov/htdocs/ICCVAM/ICCVAM.htm. ICCVAM was subsequently established in a collaborative effort by NIEHS and 13 other Federal regulatory and research agencies and programs. The Committee's functions include the coordination of interagency reviews of toxicological test methods and communication with stakeholders throughout the process of test method development and validation. The following Federal regulatory and research agencies and organizations are participating in this effort:

- Consumer Product Safety Commission
- Department of Defense
- Department of Energy
- Department of Health and Human Services
  - Agency for Toxic Substances and Disease Registry
  - Food and Drug Administration
  - National Institutes of Health
    - National Cancer Institute
    - National Institute of Environmental Health Sciences
    - National Library of Medicine
- National Institute for Occupational Safety and Health/CDC
- Department of the Interior
- Department of Labor
  - Occupational Safety and Health Administration
- Department of Transportation
  - Research and Special Programs Administration
- Environmental Protection Agency

The Corrositex® assay was proposed to ICCVAM for consideration as an *in vitro* method for use in determining the dermal corrosivity potential of chemicals. The test method submission was prepared by In Vitro International, Inc. (IVI). Independent peer review is an essential prerequisite for consideration of a method for regulatory acceptance (NIEHS, 1997). The PRP was charged with developing a scientific consensus on the usefulness of the method to generate information for human health risk assessment purposes. The proposed test method and results of the peer review will be forwarded by ICCVAM to Federal agencies for consideration. Federal agencies will determine the regulatory acceptability of the method according to their mandates.

Summary of Current Agency Requirements

Dr. Richard Hill, ICCVAM and CWG Co-Chair, presented an overview of current agency regulations with regard to dermal corrosion testing. He stated that corrosion is not universally defined, but generally focuses on destruction of the skin or the irreversability of effects on the skin. Dr. Hill further stated that testing is usually done using the *in vivo* rabbit skin corrosivity test. The test results serve as a basis for determining appropriate materials labeling and hazard identification. An international harmonization effort has been in progress in order to develop internationally consistent labeling. Measurement of pH is used to define potential corrosives, where chemicals which have a pH in the extreme ranges are considered to be potential corrosives for labeling purposes. Currently, the U. S. Department of Transportation has ac-

cepted Corrositex® as a method to determine the corrosive potential of seven chemical classes. Dr. Hill also mentioned that a tiered testing scheme has been proposed by OECD for determining dermal corrosivity potential of chemicals/products.

Overview of the Proposed Corrositex® Assay

Dr. Rosalind Wei, Director of Research and Development at IVI, described the procedure used to test chemicals or compounds using Corrositex®. The presentation was followed by assay-related questions from the PRP.

Meeting—Review of the Corrositex® Submission

Test Method Description

Dr. Harbell, the section coordinator, presented the analysis and conclusions reached by the test method description section reviewers, which included Drs. Kohrman and Stegeman.

The PRP concluded that the basis for the test was adequately described, and the protocol was complete and consistent. They further concluded that the decision rules were adequately defined, and that the range of applications is known to some degree.

Test Method Data Quality

Dr. Green, the section coordinator, presented the analysis and conclusions reached by the test method data quality section reviewers, which included Drs. Derelanko, Harbell, and Kojima.

With regard to data quality, the PRP concluded that the studies presented in the Submission were not conducted under Good Laboratory Practice (GLP) standards, but that the data were credible, based on results from two data audits. Studies conducted as part of the ECVAM prevalidation and validation studies were conducted under the "spirit" of GLP.

Test Method Performance

Dr. Hayes, the section coordinator, presented the analysis and conclusions reached by the test method performance section reviewers, which included Drs. Kohrman and Chen.

The PRP concluded that certain limitations were present in the data set (i.e., complex mixtures were not defined and thus could not be evaluated; category definitions were vague, so some could not be considered in the evaluation; and the number of chemicals in some chemical classes was limited such that performance analysis for these classes may not be representative). However, the panel concluded that the accuracy (82%), sensitivity (85%), specificity (70%), and positive and negative predictivity (78% and 80%, respectively) were adequate for the data set including the Submission, Prevalidation Study (Botham et al., 1995), and ECVAM Validation Study (Fentem et al., 1998). The PRP felt that the assay was useful as a stand-alone method for predicting the corrosive potential of acids and bases. The test can also be used as part of a tier assessment approach for determining the dermal corrosion potential of substances in other chemical classes.

Test Method Reliability

Dr. Fentem, the section coordinator, presented the analysis and conclusions reached by the test method reliability section reviewers, which included Drs. Chen and Sauder.

The PRP concluded that the reproducibility of the test was adequate, although one peer reviewer felt that additional interlaboratory investigations would be helpful. The PRP suggested

the inclusion of positive and negative controls and analysis of variance in future intra- and inter-laboratory evaluations.

Other Literature and Scientific Reviews

Dr. Derelanko, the section coordinator, presented the analysis and conclusions reached by the other literature and scientific reviews section reviewers, which included Dr. Kojima.

Key papers evaluated are listed below:

- Gordon, V. C., Harvell, J.D., and Maibach H.I. (1994) Dermal Corrosion, the Corrositex® System: A DOT Accepted Method to Predict Corrosivity Potential of Chemicals. In: A. Rougier, A. M. Goldberg, and H. I. Maigach (Eds.), In Vitro Skin Toxicology—Irritation, Phototoxicity, Sensitization. Alternative Methods in Toxicology. Mary Inn Liebert, New York. p.p. 37-45.
- Botham, P.A., Chamberlain, M., Barratt, M.D., Curren, R.D., Esdaile, D.J., Gardner, J.R., Gordon, V.C., Hildebrand, B., Lewis, R.W., Liebsch, M., Logemann, P., Osborne, R., Ponec, M., Régnier, J. –F., Steiling, W., Walker, A.P., and Balls, M. (1995). A Prevalidation Study on In Vitro Skin Corrosivity Testing. The Report and Recommendations of ECVAM Workshop 6. ATLA 23:219-255.
- Barratt, M.D., Brantom, P.G., Fentem, J.H., Gerner, I., Walker, A.P., and Worth, A.P. (1998). The ECVAM International Validation Study on In Vitro Tests for Skin Corrosivity. 1. Selection and Distribution of Test Chemicals. Toxicol. In Vitro 12:471-482.
- Fentem, J.H., Archer, G.E.B., Balls, M., Botham, P.A., Curren, R.D., Earl, L.K., Esdaile, D.J., Holzhütter, H. –G., and Liebch, M. (1998). The ECVAM International Validation Study on In Vitro Tests for Skin Corrosivity. 2. Results and Evaluation by the Management Team. Toxicol. In Vitro 12:483-524.

The PRP concluded that generally, the results reported in these papers were similar to those presented in the Submission. It was noted that the Gordon et al. (1994) publication was not peer reviewed.

Presentation of Corrositex® Performance Compared to the pH Test

Dr. Tom Goldsworthy, NICEATM, presented the findings of an evaluation of the performance of pH compared to that of Corrositex®; both tests were compared against *in vivo* rabbit skin corrosivity data as the standard. The analysis found that both the pH and Corrositex® tests are adequate for identifying the corrosive potential of chemicals with a pH value in the extreme ranges (i.e., pH less than or equal to 2 or greater than or equal to 11.5). However, Corrositex® was slightly but consistently more predictive than pH for chemicals with a pH value in the extreme ranges. Further, Corrositex® correctly identified several non-corrosive chemicals with pH values in the extreme ranges; these chemicals would be false positive calls if analyzed only by pH. Additionally, a number of chemicals with pH values in the non-extreme range (i.e., pH greater than 2 and less than 11.5) were identified as corrosive using the *in vivo* test; Corrositex® correctly identified the majority of these compounds. Given the ease and cost effectiveness of conducting a pH test, the PRP recommended that pH testing be conducted prior to the use of Corrositex®. Such information could be used in the future to re-evaluate the agreement between pH and Corrositex® in identifying corrosivity.

Summary of Non-Qualifying Chemicals

Ms. Karen Haneke, NICEATM, presented an overview of available data on non-qualifying chemicals, focusing on non-qualifying test materials for which there was also pH and *in vivo* data. Of the 75 non-qualifying test materials identified in published sources and a 1996 Corrositex® submission, 85% of these materials were considered non-corrosive according to *in vivo* test results. pH data were found for 50 non-qualifying materials, of which all but one were in the pH range of 3 to 10. pH distribution was similar when the database of nonqualifiers was limited to only test materials for which both pH and in vivo data was available (N = 33); when this limited data set was evaluated, 91% of the chemicals were non-corrosive according to *in vivo* tests.

Other Considerations and Related Issues

Dr. Stegeman, the section coordinator, presented the analysis and conclusions reached by the other considerations and related issues section reviewers, which included Dr. Sauder.

The PRP noted several advantages of the Corrositex® test compared to the *in vivo* rabbit skin corrosivity test. Corrositex® is a non-animal test that is also relatively quick and easy to perform. The PRP stated that the large proportion of test materials that do not qualify for testing by the Corrositex® method is one limitation of the assay.

The PRP also agreed that the assay, whether used alone or as a component of a tiered assessment approach, provides for the reduction and replacement of animal use for certain defined chemical classes. Additionally, chemicals that test negative or do not qualify for the Corrositex® test have a low likelihood of causing corrosive lesions if tested in animals. Any follow-up tests using *in vivo* methods could employ small numbers of animals and test agent dilution schemes to minimize numbers of animals and possible distress in any individual animal.

Public Comments

Dr. Rodger Curren, Institute for In Vitro Sciences, stated that since this is only the second ICCVAM review, the review is a precedent-setting activity. The PRP must determine whether the use of Corrositex® would provide an equivalent level of protection compared to the currently accepted *in vivo* rabbit skin corrosivity test. Dr. Curren added that with regard to reproducibility, he felt that data from only a few labs was adequate because there are performance standards (i.e., positive and negative controls). To address a PRP discussion on the adequacy of evaluating interlaboratory data from only three labs, with one being naïve, Dr. Curren stated that none of the labs were naïve; they all had experience in conducting the test. In response to the PRP's comment that the number of chemicals for some classes was inadequate for performance assessment purposes, he mentioned the difficulty in obtaining adequate *in vivo* data for comparison.

Dr. Alan Goldberg, Johns Hopkins University, asked two questions to members of the PRP panel. First, he asked for clarification on the statement that auditors concluded that the discrepancies did not affect the conclusions reached from the data. Dr. Green responded that the data deficiencies and missing data were very few, and were thus determined to have minimal effect. Second, Dr. Goldberg noted that one of the data sources evaluated (submissions and published sources) was slightly different in performance compared to the others, and asked how that would affect the totality of the data. Dr. Kohrman stated that the variability probably deals with small sample size. Dr. Goldsworthy added that evaluations were done on a wide

variety of sources and combinations thereof, and generally, the data sets were found to be similar to each other.

Dr. Katherine Stitzel, Procter & Gamble, felt that the panel should give additional thought to the statement that 20 chemicals per class would be an adequate number for evaluation. She stated that this may be setting a precedent that may be difficult to meet, strictly based on the prevalence of some chemical classes. She further added that making such a statement may be setting a standard for the *in vitro* test that was not set for the *in vivo* test.

Dr. Errol Zeiger, NIEHS, made additional comment on the issue of prevalence and how many chemicals are needed for an adequate evaluated. He pointed out that when speaking of prevalence, the discussion is not the prevalence of chemicals classes in the universe, but rather the prevalence of chemical classes in specific industries. Dr. Zeiger noted that the prevalence of certain chemical classes thus changes based on the industry evaluated and the endpoint of interest. Dr. Zeiger also provided comment on the issue of the interlaboratory reliability study and how dependent and nonindependent labs play a role in these types of assessments. He stated that one method of assessment is to include only labs with experience in conducting the assay, while a second is to include only labs with limited experience with the assay. Dr. Zeiger felt that the equivalence of training among the three labs is an asset to the evaluation, and urged caution in evaluating how labs are determined to be dependent versus independent.

Dr. Francis Kraszewski, the Gillette Company, asked if the panel was satisfied with the mechanistic basis of the assay. Dr. Hayes clarified that the test is not mechanistically based, but instead is significantly correlated.

Dr. David Hattan, Food and Drug Administration, asked, from a regulatory standpoint, whether the PRP felt that the results on neat materials could be translated to reflect the response of final formulations. Dr. Kohrman replied that the answer was dependent on what is known about the matrix. She stated that with proper information, it is possible to make an assessment of the entire mixture based on results found using neat materials. Dr. Sauder added that the question is very valid, and that information/studies pertinent to the topic would be helpful.

Dr. Ben Gregg, Environmental Protection Agency, stated that most materials reviewed by his agency are mixtures, and that EPA may be interested in using Corrositex® as a replacement for *in vivo* testing of mixtures. He stated that more work should be directed toward how the test performs for mixtures.

Dr. Robert Bronaugh, Food and Drug Administration, asked for clarification from the PRP about the database, and whether it is considered adequate versus inadequate. Dr. Scala answered that the database is considered to be adequate, but that data for certain chemical classes may be inadequate due to the few numbers of chemicals in those classes.

Peer Review Panel Conclusions

Based on their review, the PRP concluded that the Corrositex® method is equivalent to the *in vivo* rabbit skin corrosivity test for predicting corrosivity and noncorrosivity for specified chemical classes (i.e., primarily acids and bases). Therefore the test may be used either as a stand-alone assay for determining the dermal corrosion potential of acids or bases or as part of a tier assessment approach for determining the dermal corrosion potential of substances in other chemical classes.